Brain Creatine Deficiency Treatment: Long Term Brain 1H and 31P MRS Monitoring Study Under Different Creatine Regimen

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INTRODUCTION

The optimal amount of Cr-intake for treatment of brain Cr-deficiency syndromes is yet matter of debate since brain Cr-uptake, distribution and utilization is not completely explained. MRS is the only means to approach this topic since it can measure "in vivo" many metabolites directly related to brain energetics. Brain clinical spectroscopy includes ^{1}HMRS (which measures the cytosolic-soluble Cr and PCr fractions) and ^{31}P MRS (which measures high energy phosphates such as PCr, Pi, ATP and ADP).

We present and compare the time behaviour of brain Cr-restoration assessed by consecutive ^{1}H and ^{31}P MRS studies, performed during a long term Cr-intake at different doses in one patient with Arginine:Glycine AmidinoTransferase deficiency (AGAT-d) and in one patient with GuanidinoAcetate MethylTransferase deficiency (GAMT-d).

MATERIAL AND METHODS

MRS studies were performed with a 1.5T clinical scanner (LX Signa Horizon 1.5 GE, Milwaukee, WI, USA). ^{1}H spectra were acquired using a SingleVoxel STEAM short-TE sequence (TR=2010 ms, TE=30 ms, mixing time=13.7 ms, 128 averages, VOI dimension=3.4 cc) and absolute brain Cr-content was calculated using LCmodel software (Provencher S.W., Mag Reson Med 30: 672-9,1993; Helmes G. Magn Res Imaging 17(8):1211-8, 1999).

Whole brain ^{31}P MRS was recorded thought a transmit/receive surface coil using a short-TE slice selective spin echo sequence(TR= 4000 ms, TE= 25 ms, 128 averages, flip angle =60°) centering the slab in the plane through the splenium.

PCr, Pi and ATP were quantified using the PDE (phosphodiesters) peak as internal reference since its amplitude value remains stable both in normal subjects and in patients with abnormal brain energetics (Rango et al, J Cereb Flow Metab, 21:85-91, 2001).

^{1}H MRS monitoring: One 6 year-old male with AGAT-d was investigated after 1,3,6,9,12 and 24 months of 400mg/Kg/die of continuous Cr-intake (Fig.1, red line) and after a 3 months of wash-out period followed by a 3 and 6 months period of 400mg Cr-intake and after 3 and 6 months of halved therapy, i.e.200mg/kg/die (Fig.3a). One 7 year-old male with GAMT-d was investigated after 1,3,6, 9,12 months of 400mg/Kg/die Cr-therapy and after 12 months of 800mg/kg/die Cr assumption (Fig.1, blue line).

^{31}P MRS monitoring: The AGAT-d patient was evaluated with brain ^{31}P MRS after the 3-months of wash-out period, after the following 3 and 6 months of 400mg/kg/die Cr-re-intake (Fig.2a) and after 3 and 6 months of halved therapy (Fig. 3b).

The GAMT-d patient was instead assessed only after the 12 months of Cr over-intake (Fig.2b).

RESULTS and CONCLUSIONS

Results are summarized in the figures below. They demonstrated that the time-course of total brain Cr-replenishment, assessed by ^{1}HMRS, has the same biphasic trend both in AGAT-d and GAMT-d but different restoration degrees are reached with the same Cr-diet (corresponding to 90% in AGAT-d and 80% in GAMT-d). Cr-restoration of GAMT-d may increase up to 90% when doubling standard doses (Fig.1). In spite of this apparent amelioration, ^{31}PMRS performed in AGAT-d (Fig.2a) and in GAMT-d (Fig.2b), respectively under a 400mg and 800mg treatment, shows that brain PCr in GAMT-d remains markedly lower than in AGAT-d, also when total Cr-concentration is 90% of normal. Figure 3 describes the fluctuations of brain Cr-content when halving the standard dose of Cr-intake, assessed at the same interval times with ^{1}H and ^{31}PMRS in AGAT-d child: the total Cr measured by ^{1}HMRS did not significantly decrease after 6 months of halved therapy (Fig.3a) whilst ^{31}PMRS shows a dramatic drop of brain PCr when using this regimen (Fig3b). Brain Pi content did not presented any significant change in both syndromes, at any Cr-diet modifications.

These results lead to the opinion that Cr-therapeutic range is included between 300-400mg/Kg/die, which corresponds to the most common regimen suggested as nutritional supplement in athletes.

This study also demonstrates that the rate of the Cr-phosphorilation via creatine-kinase/creatine-phosphate (CK/CrP) system in the brain is not directly related to the cytosolic concentration of Cr and that ^{31}P MRS is more suitable than ^{1}HMRS in the long term treatment evaluation of brain Cr-deficiency syndromes.

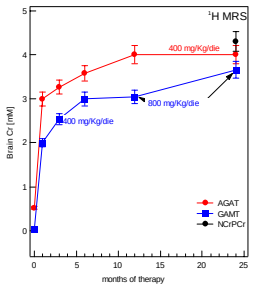

Fig 1

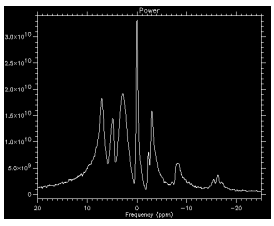

Fig.2a

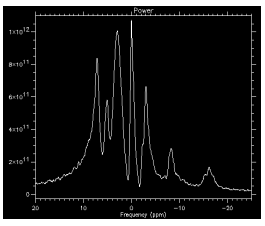

Fig.2b

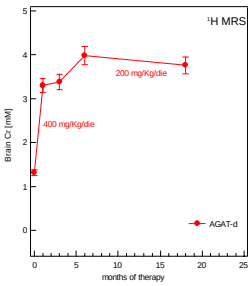

Fig 3a

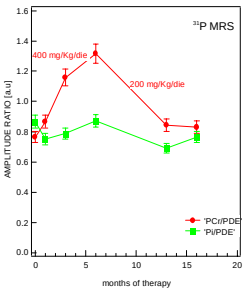

Fig3b